

<b>INFORMATION DISCLOSURE STATEMENT</b>	Atty. Docket No.: 00403.CN1	Serial No.: 10/028,224
	Applicant(s): Benson et al.	Confirmation No.: 4497
	Application Filing Date: Dec. 21, 2001	Group: 1652
	Information Disclosure Statement mailed: <b>FEBRUARY 12, 2003</b>	

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**U.S. PATENT DOCUMENTS**

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
DS	2003/0095958 A1	05/22/03	Bhisetti et al.	/	/	

**FOREIGN PATENT DOCUMENTS**

Examiner Initial	Document Number	Date	Country	Class	Subclass	Translation	
						Yes	No
	NONE						

**OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)**

Examiner Initial	Document Description
DS	Drenth, "Principles of Protein X-ray Crystallography," Second Edition, 1994 Springer-Verlag New York, Inc., pages 1-18.

**EXAMINER**

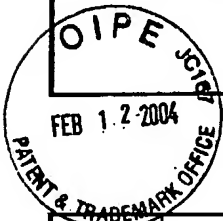
DS

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## U.S. PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
DS	5,744,346	04/28/98	Chrysler et al.	/	/	
DS	5,942,400	08/24/99	Anderson et al.	/	/	
DS	6,297,021 B1	10/02/01	Nienaber et al.	/	/	
DS	6,420,534 B1	07/16/02	Gurney et al.	/	/	
DS	6,440,698 B1	08/27/02	Gurney et al.	/	/	
DS	2002/0037315 A1	03/28/02	Gurney et al.	/	/	
DS	2002/0049303 A1	04/25/02	Tang et al.	/	/	
DS	2002/0055459 A1	05/09/02	Chopra et al.	/	/	
DS	2002/0064819 A1	05/30/02	Gurney et al.	/	/	
DS	2002/0081634 A1	06/27/02	Gurney et al.	/	/	
DS	2002/0115600 A1	08/22/02	Koelsch et al.	/	/	

## FOREIGN PATENT DOCUMENTS

Examiner Initial	Document Number	Date	Country	Class	Subclass	Translation	
						Yes	No
DS	WO 01/17369 A2	03/30/00	PCT	/	/		
DS	WO 01/49097 A2	07/12/01	PCT	/	/		
DS	WO 02/053594 A2	07/11/02	PCT	/	/		
DS	WO 02/25276 A1	03/28/02	PCT	/	/		

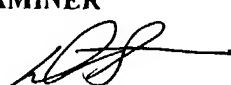
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EXHIBIT A

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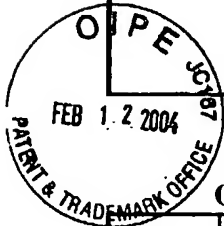
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**OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)**

Examiner Initial	Document Description
DS	Brünger, "X-PLOR: Version 3.1, a System for X-Ray Crystallography and NMR", Yale University Press, New Haven & London, 1992; cover page, publication page and table of contents: 13 pages.
DS	Brünger et al., "Slow-cooling protocols for crystallographic refinement by simulated annealing," <i>Acta Crystallogr A</i> . 1990 Jul 1;46( Pt 7):585-93.
DS	"CNX: Crystallography and NMR eXplorer" datasheet, Accelrys Corporate Headquarters, San Diego, CA (2001). [ retrieved August 30, 2002 from the Internet: <URL: <del>http://www</del> .accelrys.com>; 2 pgs.]
DS	Epps et al., "The ligand affinity of proteins measured by isothermal denaturation kinetics," <i>Anal Biochem</i> . 2001 May 1;292(1):40-50.
DS	Otwinowski, "Maximum Likelihood Refinement of Heavy Atom Parameters," <i>Isomorphous Replacement and Anomalous Scattering</i> , Wolf et al., eds., Science & Engineering Research Council, Daresbury Laboratory, Warrington, U.K., Proceedings of the CCP4 Study Weekend, 25-26 Jan. 1991; pages 80-86.
DS	Research Collaboratory for Structural Bioinformatics, "Protein Data Bank," [online] United States; retrieved August 30, 2002 from the Internet: <URL: <del>http://www</del> .rcsb.org/pdb/> 8 pages.

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DS	6,221,645 B1	04/24/01	Chrysler et al.	/	/	
DS	6,225,103 B1	05/01/01	Keolsch et al.	/	/	
DS	6,245,884 B1	06/12/01	Hook	/	/	
DS	6,258,386 B1	06/10/01	Xia et al.	/	/	
DS	6,268,158 B1	07/31/01	Pantoliano et al.	/	/	
DS	2001/0016324 A1	08/23/01	Gurney et al.	/	/	
DS	2001/0018208 A1	08/30/01	Gurney et al.	/	/	
DS	2001/0021391 A1	09/13/01	Gurney et al.	/	/	
DS	6,291,223 B1	09/18/01	Christie et al.	/	/	
DS	6,329,163 B1	12/11/01	Anderson et al.	/	/	

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Examiner Initial	Document Number	Date	Country	Class	Subclass	Translation	
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DS	WO 01/00663 A2	01/04/01	PCT	/	/		
DS	WO 01/00665 A2	01/04/01	PCT	/	/		
DS	WO 01/23533 A2	04/05/01	PCT	/	/		
DS	WO 01/49098 A2	07/12/01	PCT	/	/		
DS	WO 01/50829 A2	07/19/01	PCT	/	/		

**OTHER DOCUMENTS (Including Authors, Title, Date, Pertinent Papers, etc.)**

Examiner Initial	Document Description
DS	Bartlett et al., "CAVEAT: A program to facilitate the structure-derived design of biologically active molecules," <i>Molecular Recognition: Chemical and Biological Problems</i> , Royal Society of Chemistry, Special Pub No. 78:182-196 (1989).
DS	Benson et al., "An enzyme-substrate complex involved in bacterial cell wall biosynthesis," <i>Nat Struct Biol.</i> 1995 Aug;2(8):644-53.

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DS	Berman et al., "The Protein Data Bank," <i>Nucleic Acids Res.</i> 2000 Jan 1;28(1):235-42.
DS	Blundell et al., <i>Protein Crystallography</i> , Academic Press, New York, NY; title page, publication page, and table of contents only, 8 pages (1976)
DS	Böhm, "The computer program LUDI: a new method for the de novo design of enzyme inhibitors," <i>J Comput Aided Mol Des.</i> 1992 Feb;6(1):61-78.
DS	Collaborative Computational Project, No. 4, "The CCP4 suite: programs for protein crystallography" <i>Acta Cryst.</i> 1994;D50:760-3.
DS	Eisen et al., "HOOK: a program for finding novel molecular architectures that satisfy the chemical and steric requirements of a macromolecule binding site," <i>Proteins: Struct. Funct. Genet.</i> 1994 Jul;19(3):199-221.
DS	Ermolieff et al., "Proteolytic activation of recombinant pro-memapsin 2 (pro-beta-secretase) studied with new fluorogenic substrates," <i>Biochemistry.</i> 2000 Oct 10;39(40):12450-6.
DS	Fairlie et al., "Conformational selection of inhibitors and substrates by proteolytic enzymes: implications for drug design and polypeptide processing," <i>J Med Chem.</i> 2000 Apr 6;43(7):1271-81.
DS	Finzel, "LORE: exploiting database of known structures," <i>Meth. Enzymol.</i> 1997; 277(B):230-42.
DS	Gillet et al., "SPROUT: a program for structure generation," <i>J Comput Aided Mol Des.</i> 1993 Apr;7(2):127-53.
DS	Goodford, "A computational procedure for determining energetically favorable binding sites on biologically important macromolecules," <i>J Med Chem.</i> 1985 Jul; 28(7):849-57.
DS	Goodsell et al., "Automated docking of substrates to proteins by simulated annealing," <i>Proteins: Struct. Funct. Genet.</i> 1990;8(3):195-202.
DS	Haniu et al., "Characterization of Alzheimer's beta -secretase protein BACE. A pepsin family member with unusual properties," <i>J Biol Chem.</i> 2000 Jul 14;275(28):21099-106.
DS	Hendrickson et al., "Selenomethionyl proteins produced for analysis by multi-wavelength anomalous diffraction (MAD): a vehicle for direct determination of three-dimensional structure," <i>EMBO J.</i> 1990 May;9(5):1665-72.


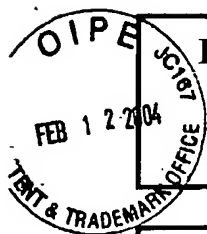
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DS	Hong et al., "Structure of the protease domain of memapsin 2 ( $\beta$ -secretase) complexed with inhibitor," <i>Science</i> . 2000 Oct 6;290(5489):150-3.
DS	Huang et al., "A 3D-structural model of memapsin 2 protease generated from theoretical study," <i>Acta Pharmacol Sin</i> . 2001 Jan;22(1):50-56.
DS	Hussain et al., "Identification of a novel aspartic protease (Asp 2) as $\beta$ -secretase," <i>Mol Cell Neurosci</i> . 1999 Dec;14(6):419-27.
DS	Jiang et al., "Protein hydration observed by X-ray diffraction. Solvation properties of penicillopepsin and neuraminidase crystal structures," <i>J Mol Biol</i> . 1994 Oct 14;243(1):100-15.
DS	Kang et al., "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," <i>Nature</i> . 1987 Feb 19;325(6106):733-6.
DS	Kitaguchi et al., "Novel precursor of Alzheimer's disease amyloid protein shows protease inhibitory activity," <i>Nature</i> . 1988 Feb 11;331(6156):530-2.
DS	Kuntz et al., "A geometric approach to macromolecule-ligand interactions," <i>J Mol Biol</i> . 1982 Oct 25;161(2):269-88.
DS	Lattman, "Use of the rotation and translation functions," <i>Methods Enzymol</i> . 1985;115:55-77.
DS	Lauri et al., "CAVEAT: a program to facilitate the design of organic molecules," <i>J Comput Aided Mol Des</i> . 1994 Feb;8(1):51-66.
DS	Lin et al., "Human aspartic protease memapsin 2 cleaves the $\beta$ -secretase site of $\beta$ -amyloid precursor protein," <i>Proc Natl Acad Sci U S A</i> . 2000 Feb 15;97(4):1456-60.
DS	Mallender et al., "Characterization of recombinant, soluble beta-secretase from an insect cell expression system," <i>Mol Pharmacol</i> . 2001 Mar;59(3):619-26.
DS	Martin, "3D database searching in drug design," <i>J Med Chem</i> . 1992 Jun 12;35(12):2145-54.
DS	Meng et al., "Automated docking with grid-based energy evaluation," <i>J. Comp. Chem</i> , 1992 May;13(4):505-524.
DS	Miranker et al., "Functionality maps of binding sites: a multiple copy simultaneous search method," <i>Proteins: Struct. Funct. Genet</i> . 1991;11(1):29-34.

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DS	National Institutes of Health, "BLAST 2 Sequences," [online] United States; retrieved August 29, 2001 from the Internet: <del>URL:</del> <a href="http://www.ncbi.nlm.nih.gov/gorf/bl2.html">http://www.ncbi.nlm.nih.gov/gorf/bl2.html</a> , 1 pg.
DS	Navaza, "AMoRe: an automated package for molecular replacement," <i>Acta Cryst.</i> 1994;450:157-163.
DS	Nishibata et al., "Automatic creation of drug candidate structures based on receptor structure. Starting point for artificial lead generation," <i>Tetrahedron</i> , 1991;47(43):8985-90.
DS	Noren et al., "A general method for site-specific incorporation of unnatural amino acids into proteins," <i>Science</i> . 1989 Apr 14;244(4901):182-8.
DS	Park et al., "Molecular Characterization of Candidate $\beta$ -secretases, BACE1 and BACE2," ScholarOne, Inc. [online] Session No. 180.11; Society for Neuroscience's 30th Annual Meeting, New Orleans, LA, November 4 - 9, 2000 [retrieved on October 29, 2001]. Retrieved from the Internet URL: <del>http://sfn.scholarone.com/itin2000/main.html?new_page_id=76&amp;abstract_id=19280&amp;is_tech=0</del> , 1 page.
DS	Ponte et al., "A new A4 amyloid mRNA contains a domain homologous to serine proteinase inhibitors," <i>Nature</i> . 1988 Feb 11;331(6156):525-7.
DS	Research Collaboratory for Structural Bioinformatics, "Protein Data Bank," [online] United States; retrieved April 9, 2001 from the Internet: <del>URL:</del> <a href="http://www.rcsb.org/pdb/">http://www.rcsb.org/pdb/</a> 2 pages.
DS	Rossmann, ed., <i>The Molecular Replacement Method: A Collection of Papers on the Use of Non-Crystallographic Symmetry</i> , Intl. Sci. Rev. Ser. No. 13, Gordon & Breach, New York, NY; title page, publication page, and table of contents only, 6 pages (1972).
DS	Sack, "CHAIN - A Crystallographic Modeling Program," <i>J Molecular Graphics</i> . 1988 Dec; 6(4):224-5.
DS	Sauder et al., "Modeling of substrate specificity of the Alzheimer's disease amyloid precursor protein beta-secretase," <i>J Mol Biol.</i> 2000 Jul 7;300(2):241-8.
DS	Shi et al., "The pro domain of $\beta$ -secretase does not confer strict zymogen-like properties but does assist proper folding of the protease domain," <i>J Biol Chem.</i> 2001 Mar 30;276(13):10366-73.

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DS	Sinha et al. "Purification and cloning of amyloid precursor protein $\beta$ -secretase from human brain," <i>Nature</i> . 1999 Dec 2;402(6761):537-40.
DS	Skovronsky et al., "Beta-secretase revealed: starting gate for race to novel therapies for Alzheimer's disease," <i>Trends Pharmacol Sci</i> . 2000 May;21(5):161-3.
DS	Tanzi et al. "Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease," <i>Nature</i> . 1988 Feb 11; 331(6156): 528-30.
DS	Tatusova et al., "BLAST 2 Sequences, a new tool for comparing protein and nucleotide sequences," <i>FEMS Microbiol Lett</i> . 1999 May 15;174(2):247-50.
DS	Travis, "Proteins and organic solvents make an eye-opening mix," <i>Science</i> . 1993 Nov 26;262(5138):1374.
DS	Turner et al., "Substrate specificity of memapsin 2 (beta-secretase): Basis for inhibitor drug design for Alzheimer's disease," Experimental Biology 2001 Conference. Orlando, Florida, USA. March 31-April 4, 2001. Abstracts, part I. <i>FASEB J</i> . 2001 Mar 7;15(4):A538.
DS	Van Duyne et al., "Atomic structures of the human immunophilin FKBP-12 complexes with FK506 and rapamycin," <i>J Mol Biol</i> . 1993 Jan 5;229(1):105-24.
DS	Vassar et al. "B-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE," <i>Science</i> . 1999 Oct 22;286(5440):735-41.
DS	Wyckoff et al., eds., <i>Methods in Enzymology Vol. 114 - Diffraction Methods for Biological Macromolecules</i> , Academic Press, Orlando, FL; title page, publication page, and table of contents only, 5 pages (1985).
DS	Wyckoff et al., eds., <i>Methods in Enzymology Vol. 115. Diffraction Methods for Biological Macromolecules</i> , Academic Press, Orlando, FL; title page, publication page, and table of contents only, 4 pages (1985).
DS	Yan et al. (1999), "Membrane-anchored aspartyl protease with Alzheimer's disease $\beta$ -secretase activity," <i>Nature</i> . 1999 Dec 2;402(6761):533-7.

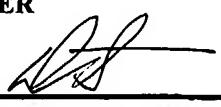
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